Review of: "Voluntary Exercise Prevents Hypertensive Response Sensitization Induced by Angiotensin II"

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Commentary: Voluntary Exercise Prevents Hypertensive Response Sensitization Induced by Angiotensin II

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A commentary on

Voluntary Exercise Prevents Hypertensive Response Sensitization Induced by Angiotensin II

By Xue B, Cui J-L, Guo F, Beltz TG, Zhao Z-G, Zhang G-S and Johnson AK (2022) Voluntary Exercise Prevents Hypertensive Response Sensitization Induced by Angiotensin II. Front. Neurosci. 16:848079. doi: 10.3389/fnins.2022.848079

Hypertension is a major risk factor for cardiovascular diseases such as heart failure, chronic renal disease, and stroke, affecting more than 31% adults worldwide(Tsao et al., 2022){Tsao, 2022 #75}. Hypertensive response sensitization (HTRS) involves neuroplasticity induced by a wide range of physiological and behavioural challenges occurring throughout life(Johnson and Xue, 2018). However, little is known about the detail mechanism of the occurrence of HTRS, which may contribute to the pathogenesis of essential hypertension. It has been reported that cellular and molecular changes that mediate HTRS are located and maintained in the central neural network. Furthermore, these changes occur mainly in the nuclei involved in controlling and maintaining the activity of the sympathetic nervous system(Dampney, 2016; Xue et al., 2022). However, there is lack of special strategies for attenuating the HTRS in hypertension. Exercise training exerts cardiovascular protection, which has profound effects on the renin-angiotensin system (RAS), inflammatory cytokines, glutamatergic input to cardiovascular centers, and oxidative stress, all of which affect autonomic nervous system activity and regulate blood pressure in both physiological and pathophysiological states(Zha et al., 2013; Ren et al., 2016; Farah et al., 2021). And therefore, it is of great significance for the prevention and treatment of hypertension to clarify the mechanism by which exercise training blocks the HTRS through the central mechanism.

Xue and his colleagues aimed to test the hypothesis that voluntary exercise training would protect against subpressor Angiotension II (ANG II)-induced HTRS via alterations in brain RAS activity, inflammation, and oxidative stress. Adult male rats were given access to either “blocked” (sedentary rats) or functional running (exercise rats) wheels for 12 weeks. The Induction-Delay-Expression (I-D-E) paradigm was applied for the rats during the last 4 weeks of the sedentary vs.

exercise conditions. During I paradigm, a low sub-pressor dose of ANG II or saline was delivered subcutaneously by osmotic minipump for 1 week. The rats then rested for 1 week (D paradigm), after which time, another pump were implanted to deliver a slow-pressor dose of ANG II for 2 weeks (E paradigm). This experimental approach allowed assessment of the effect of voluntary exercise training on the induction of HTRS by pretreatment with a low sub-pressor dose of ANG II during I paradigm and expressed during E paradigm by administering a slow-pressor dose of ANG II. Running distances, metabolic markers and changes in blood pressure were determined during voluntary running and I-D-E paradigm. Putative central nervous system molecular and cellular mediators including RAS components, inflammatory and oxidative stress markers in key brain structures were also measured. The experimental results provide further evidence that exercise training blocks the sensitized hypertensive response through central mechanisms acting to alter activity in brain cardiovascular nuclei.

There were three major findings. First, a systemic subpressor dose of ANG II pretreatment elicited HTRS to a subsequent infusion of a slow-pressor dose of ANG II in sedentary rats, which were mediated by increased centrally driven sympathetic tone. However, this augmentation of the hypertensive response and sympathetic tone was not exhibited by the exercised rats. Second, the subpressor dose of ANG II infusion during I paradigm resulted in a significant increase in mRNA expression of several prohypertensive components such as angiotensin II type 1 receptor (AT1-R), angiotensin converting enzyme, NADPH oxidase 2, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in key cardiovascular brain region when they were measured at the end of D paradigm. Third, the exercise abolished the upregulated expression of most of the prohypertensive components, and upregulated mRNA expression of some antihypertensive components including interleukin-10 (IL-10), angiotensin II type 2 receptor (AT2-R), and Mas receptor (Mas-R). This suggested that the exercise plays a beneficial role in preventing HTRS, which is associated with reduced expression of prohypertensive components of the RAS, proinflammatory cytokines, and NADPH oxidase and with enhanced expression of antihypertensive components of the RAS and anti-inflammatory cytokine in the central nervous system.

This study elucidates the molecular mechanisms involved in the sensitized hypertensive response induced by ANG II infusion and confirms that voluntary exercise attenuates HTRS induced by ANG II infusion. This study clarifies the relationship between HTRS and essential hypertension from the perspective of neuroplasticity, which provides a new content for the pathogenesis of hypertension. In addition, this study also explores a strategy to improve HTRS through voluntary exercise, and provides a new theoretical basis for the prevention and treatment of hypertension.

However, several limitations should be noted. First, there is no doubt that the hypothalamic paraventricular nucleus (PVN) involves in sympathetic activity and blood pressure regulation, but the PVN also controls food intake, appetite, cerebral blood flow, and body temperature. Nevertheless, we still do not know whether a subset of PVN neurons is dedicated to specifically participating in HTRS in this study. In addition, sympathetic tone to the circulatory system is regulated by subsets of presympathetic neurons in the rostral ventrolateral medulla (RVLM). Brain stem regions such as the RVLM, solitary tract nucleus (NTS), and caudal ventrolateral medulla (CVLM) are clearly as important as the PVN to blood pressure control and deserve far more attention in the context of HTRS. Second, a sub-pressor dose of ANG II upregulated the mRNA level of AT1-R in both the lamina terminalis (LT) and PVN. However, voluntary exercise reversed upregulated mRNA expression of AT1-R only in the PVN. However, it is not clear that there is a causal relationship

between these molecular changes in brain cardiovascular nuclei and alterations in sensitization of hypertension and sympathetic tone.

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WZ Wang was accountable for all aspects of this commentary. XT contributed to write this commentary.

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Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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